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SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: Dwayne C. Jones Examiner # : _____ Date: 27 FEB01

Art Unit: 614 Phone Number 30 Y-4674 Serial Number: 09/58[illegible]

Mail Box and Bldg/Room Location: 1001 207 Results Format Preferred (circle): PAPER DISK E-MAIL

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Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: Mc Arthur

Inventors (please provide full names): _____

Earliest Priority Filing Date: 27 APR 1999

***For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.**

Please search generic claim 1
claim 10 and
the compound of claim 15

claim 3 - Please give examples of age-related behavioral disorders.

POINT OF CONTACT:
BARB O'BRYEN
TECH. INFORMATION SPECIALIST
STIC CM1 12C14 308-4291

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PTO-1590 (1-2000)

expts.) using microdialysis and behavioral techniques. Twenty-four after the last treatment, cortical ACh levels were significantly hig rats subchronically treated with HEP than in rats treated with saline AChE activity was still inhibited in cortex, hippocampus and striatum. The injection of a challenge dose of HEP (0.6 mg/kg s.c.) 24 h after the last treatment produced a faster and a more sustained increase of ACh in the cortex of subchronically treated rats compared to those repeatedly injected with saline. However, the max. increase of ACh levels after injection of the challenge was comparable in both groups. In an object recognition test in which the pretest and test phase were spaced by 45 days, HEP prevented the deterioration of spatial memory occurring during this period, but had no effect on non-spatial memory. The present results suggest that moderate inhibition of brain AChE is able to maintain high levels of cortical extracellular ACh in aged rats and that this increase matches facilitatory effect of HEP on spatial memory.

IT **9000-81-1, Acetylcholinesterase**
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(effect of subchronic treatment with the **acetylcholinesterase inhibitor** heptastigmine on central cholinergic transmission and memory impairment in aged rats)

L164 ANSWER 46 OF 71 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:533469 CAPLUS
DOCUMENT NUMBER: 129:254877
TITLE: Effect of subchronic treatment with metrifonate and tacrine on brain cholinergic function in aged F344 rats
AUTHOR(S): Giovannini, Maria Grazia; Scali, Carla; Bartolini, Luciano; Schmidt, Bernard; Pepeu, Giancarlo
CORPORATE SOURCE: Department of Preclinical and Clinical Pharmacology, University of Florence, Florence, 50134, Italy
SOURCE: Eur. J. Pharmacol. (1998), 354(1), 17-24
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The effects of 21-day treatment with the acetylcholinesterase inhibitors metrifonate (80 mg kg-1 per os (p.o.)) and tacrine (3 mg kg-1 p.o.), twice daily, on cortical and hippocampal cholinergic systems were investigated in aged rats (24-26 mo). Extracellular acetylcholine levels were measured by transversal microdialysis in vivo; choline acetyltransferase and acetylcholinesterase activities were measured ex vivo by radiometric methods. Basal cortical and hippocampal extracellular acetylcholine levels, measured 18 h after the last metrifonate treatment, were about 15 and two folds higher, resp., than in control and tacrine-treated rats. A challenge with metrifonate further increased cortical and hippocampal acetylcholine levels by about three and four times, resp. Basal extracellular acetylcholine levels, measured 18 h after the last treatment with tacrine were not statistically different from those of the control rats. A challenge with tacrine increased cortical and hippocampal extracellular acetylcholine levels by about four and two times. A 75% inhibition of cholinesterase activity was found 18 h after the last metrifonate administration, while only a 15% inhibition was detectable 18 h after the last tacrine administration. The challenge with metrifonate or tacrine resulted in 90 and 80% cholinesterase inhibition, resp. These results demonstrate that in aging rats a subchronic treatment with metrifonate results in a long-lasting, cholinesterase inhibition, and a persistent increase in acetylcholine extracellular levels which compensate for the age-assocd. cholinergic hypofunction. Metrifonate is therefore a potentially useful agent for the cholinergic deficit accompanying Alzheimer's disease.

IT **9000-81-1, Acetylcholinesterase**

Searched by Barb O'Bryen, STIC 308-4291

L164 ANSWER 50 OF 71 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:735087 CAPLUS
DOCUMENT NUMBER: 128:43758
TITLE: Metrifonate improves associative learning and retention in aging rabbits
AUTHOR(S): Kronforst-Collins, M. A.; Moriearty, P. L.; Schmidt, B.; Disterhoft, J. F.
CORPORATE SOURCE: Department of Cell and Molecular Biology, Institute for Neuroscience, Northwestern University Medical School, Chicago, IL, 60611-3008, USA
SOURCE: Behav. Neurosci. (1997), 111(5), 1031-1040
CODEN: BENEDJ; ISSN: 0735-7044
PUBLISHER: American Psychological Association
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The cholinergic system is known to show deterioration during aging and Alzheimer's disease (AD). In response, a therapeutic approach to AD has been to attempt to compensate for the decrease in central cholinergic function by potentiating the activity of the remaining intact cholinergic cells with cholinesterase (ChE) inhibitors. In this study treatment with the long-lasting ChE inhibitor metrifonate facilitated acquisition and retention of eyeblink conditioning in aging rabbits. Metrifonate treatment resulted in steady-state, dose-dependent acetylcholinesterase (AChE) inhibition in red blood cells. Maximal behavioral efficacy was achieved with AChE inhibition of approx. 40%, with no further improvements resulting from increased levels of inhibition. Metrifonate was behaviorally effective in the absence of the severe side effects that can plague ChE inhibitors, supporting metrifonate as a possible treatment for the cognitive deficits resulting from normal aging and AD.
IT **9000-81-1, Acetylcholinesterase**
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(metrifonate improves associative learning and retention in aging rabbits in relation to **acetylcholinesterase inhibition** and treatment of Alzheimer's disease)

L164 ANSWER 51 OF 71 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:242145 CAPLUS
DOCUMENT NUMBER: 126:271701
TITLE: Donepezil
AUTHOR(S): Bryson, Harriet M.; Benfield, Paul
CORPORATE SOURCE: Adis International Limited, Auckland, N. Z.
SOURCE: Drugs Aging (1997), 10(3), 234-239
CODEN: DRAGE6; ISSN: 1170-229X
PUBLISHER: Adis
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 26 refs. Donepezil is a specific and potent acetylcholinesterase inhibitor according to in vitro data. It displays primarily noncompetitive inhibitory activity. In vivo, donepezil inhibited acetylcholinesterase activity in human erythrocytes and increased extra-cellular acetylcholine levels in the cerebral cortex and hippocampus of the rat. Donepezil demonstrated efficacy in tests of ref. memory in animals, but had less consistent activity in tests of working memory. Donepezil 5 or 10 mg/day was assocd. with significant improvements in cognitive function [assessed by the Alzheimer's Disease Assessment Scale - cognitive subscale (ADAS-cog)] after 14 and 30 wk and patient global function (Clinician's Interview-based Impression of Change incorporating caregiver input score) after 30 wk, compared with placebo, in patients with mild to moderate Alzheimer's disease. After 2 yr, donepezil 5 or 10 mg/day was assocd. with an ADAS-cog score approx. 4 points better than would be expected in untreated patients with mild to

moderate Alzheimer's disease. The most common adverse events reported in assocn. with donepezil 5 mg/day were gastrointestinal events (nausea/vomiting, diarrhea, gastric upset and constipation) and dizziness. No hepatotoxicity was reported after 12 wk' treatment.

IT **9000-81-1, Acetylcholinesterase**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**inhibitor**; donepezil pharmacodynamics and pharmacokinetics)

L164 ANSWER 52 OF 71 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:123307 CAPLUS
DOCUMENT NUMBER: 126:220296
TITLE: Synthesis and preliminary structure-activity relationships of 1-[(3-fluoro-4-pyridinyl)amino]-3-methyl-1H-indol-5-yl methyl carbamate (P10358), a novel **acetylcholinesterase inhibitor**
AUTHOR(S): Martin, Lawrence L.; Davis, Larry; Klein, Joseph T.; Nemoto, Peter; Olsen, Gordon E.; Bores, Gina M.; Camacho, Fernando; Petko, Wayne W.; Rush, Douglas K.; et al.
CORPORATE SOURCE: Hoechst Marion Roussel Inc., Neuroscience Therapeutic Area, Bridgewater, NJ, 08807-0800, USA
SOURCE: Bioorg. Med. Chem. Lett. (1997), 7(2), 157-162
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A series of carbamate analogs of besipirdine (HP 749) was synthesized as potential agents with enhanced cholinomimetic properties for the treatment of Alzheimer's disease. P10358, 1-[(3-fluoro-4-pyridinyl)amino]-3-methyl-1H-indol-5-yl Me carbamate, emerged as a potent, reversible acetylcholinesterase inhibitor that significantly enhanced performance on oral or parenteral administration in learning and memory paradigms.

IT **9000-81-1, Acetylcholinesterase**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(synthesis and structure-activity relationships of besipirdine carbamate analogs as **acetylcholinesterase inhibitors**
)

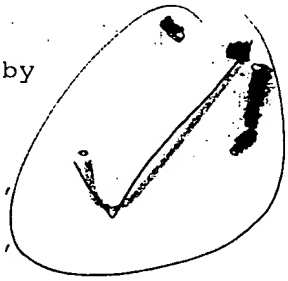
L164 ANSWER 53 OF 71 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:32874 CAPLUS
DOCUMENT NUMBER: 126:70952
TITLE: Effect of TAK-147, a novel AChE inhibitor, on cerebral energy metabolism
AUTHOR(S): Nakayama, Takahiro; Takahashi, Hideki; Miyamoto, Masaomi; Goto, Giichi; Nagai, Yasuo
CORPORATE SOURCE: Pharmaceutical Research Laboratories I, Takeda Chemical Industries, Ltd., Osaka, 532, Japan
SOURCE: Neurobiol. Aging (1996), 17(6), 849-857
CODEN: NEAGDO; ISSN: 0197-4580
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB **Effect of TAK-147, a novel acetylcholinesterase (AChE) inhibitor**, on cerebral energy metab. was investigated using an in vivo 31P-magnetic resonance spectroscopy (31P-MRS) technique and the autoradiog. 2-deoxy-[14C]-D-glucose method in aged Fischer 344 rats. We revealed that high-energy phosphate metabolites, phosphocreatine (PCr) and ATP, in the brain decreased gradually with aging and that significant decrement of cerebral PCr and ATP was obsd. from 13- and 8.5-mo-old in comparison with those of 2.5-mo-old rats, resp. Daily oral administration of TAK-147 (1 mg/kg) for 40 days increased PCr and ATP levels in aged rats (29-mo-old). To det. the site at which TAK-147 acts to increase high-energy phosphate

metab., we investigated the rate of local cerebral glucose utilization (LCGU) in various brain regions. The rate of LCGU decreased in almost all brain regions in aged rats (28 mo of age), and the decrease was significant in 29 out of the 35 regions. When TAK-147 was administered orally to the aged rats, the levels were dose dependently increased, esp. in the auditory cortex. These results indicate that TAK-147 increases cerebral energy metab. in aged rats.

IT **9000-81-1, Acetylcholinesterase**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**inhibitor**; effect of **acetylcholinesterase inhibitor** TAK-147 on cerebral energy metab. in aged rats)

L164 ANSWER 54 OF 71 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:193684 CAPLUS
DOCUMENT NUMBER: 126:207463
TITLE: Huperzine A, a novel promising **acetylcholinesterase inhibitor**
AUTHOR(S): Cheng, Dong Hang; Ren, Hua; Tang, Xi Can
CORPORATE SOURCE: State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai, 200031, Peop. Rep. China
SOURCE: NeuroReport (1996), 8(1), 97-101
CODEN: NERPEZ; ISSN: 0959-4965
PUBLISHER: Rapid Science Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English



AB The effects of huperzine A (I) on memory impairments (amnesia) induced by scopolamine (a model for human dementia) were evaluated using a radial maze task and inhibition of cholinesterase in vitro compared with the effects of E 2020 (II) and tacrine (III). Scopolamine (0.2 mg/kg) significantly impaired spatial memory in rats. I (0.1-0.4 mg/kg, p.o.), II (0.5-1.0 mg/kg, p.o.) and IIIe (1.0-2.0 mg/kg, p.o) were able to reverse these scopolamine-induced memory deficits. The ratios of I, II, and III for butyrylcholinesterase:acetylcholinesterase detd. by a colorimetric method were 884.57, 489.05, and 0.80, resp. The results demonstrated that I was the most selective acetylcholinterase inhibitor, and improved the working memory deficit induced by scopolamine significantly better than did II or III, suggesting it may be a promising agent for clin. therapy of cognitive impairment in patients with Alzheimer's disease.

IT **9000-81-1, Acetylcholinesterase**
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(huperzine A, a novel promising **acetylcholinesterase inhibitor** for clin. therapy of cognitive impairment in patients with Alzheimer's disease)

L164 ANSWER 55 OF 71 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2000037532 EMBASE
TITLE: Regulating and assessing risks of cholinesterase-inhibiting pesticides: Divergent approaches and interpretations.
AUTHOR: Carlock L.L.; Chen W.L.; Gordon E.B.; Killeen J.C.; Manley A.; Meyer L.S.; Mullin L.S.; Pendino K.J.; Percy A.; Sargent D.E.; Seaman L.R.; Svanborg N.K.; Stanton R.H.; Tellone C.I.; Van Goethem D.L.
CORPORATE SOURCE: L.L. Carlock, Toxicology and Regulatory Consulting, 6343 38th Ave. S.W., Seattle, WA 98126, United States
SOURCE: Journal of Toxicology and Environmental Health - Part B, (1999) 2/2 (105-160).
Refs: 69
ISSN: 1093-7404 CODEN: JTECFR
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
Searched by Barb O'Bryen, STIC 308-4291

Jones

hypotheses, both of which increase cortical cholinergic activity.

L164 ANSWER 25 OF 71 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1997:457426 BIOSIS
DOCUMENT NUMBER: PREV199799756629
TITLE: Pontine nitric oxide modulates acetylcholine release, rapid eye movement sleep generation, and respiratory rate.
AUTHOR(S): Leonard, Timothy O.; Lydic, Ralph (1)
CORPORATE SOURCE: (1) Dep. Anesthesia, Pennsylvania State Univ., Coll. Med., Hershey, PA 17033, USD
SOURCE: [illegible] ISSN: 0270-6474.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Pontine cholinergic neurotransmission is known to play a key role in the regulation of rapid eye movement (REM) sleep and to contribute to state-dependent respiratory depression. Nitric oxide (NO) has been shown to alter the release of acetylcholine (ACh) in a number of brain regions, and previous studies indicate that NO may participate in the modulation of **sleep/wake** states. The present investigation tested the hypothesis that inhibition of NO synthase (NOS) within the medial pontine reticular formation (mPRF) of the unanesthetized cat would decrease ACh release, inhibit REM sleep, and prevent cholinergically mediated respiratory depression. Local NOS inhibition by microdialysis delivery of NG-nitro-L-arginine (NLA) significantly reduced ACh release in the cholinergic cell body region of the pedunculopontine tegmental nucleus and in the cholino-ceptive mPRF. A second series of experiments demonstrated that mPRF microinjection of NLA significantly reduced the amount of REM sleep and the REM sleep-like state caused by mPRF injection of the [illegible] cholinesterase inhibitor, [illegible]. NLA duration but not frequency of REM sleep epochs was significantly decreased by mPRF NLA administration. Injection of NLA into the mPRF before neostigmine injection also blocked the ability of neostigmine to decrease respiratory rate during the REM sleep-like state. Taken together, these findings suggest that mPRF NO contributes to the modulation of ACh release, REM sleep, and breathing.

L164 ANSWER 26 OF 71 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1997:505567 BIOSIS
DOCUMENT NUMBER: PREV199799804770
TITLE: Tacrine response: Review of two years of prescription.
AUTHOR(S): Augry, F.; Darchy, A.; De Rotrou, J.; Guelfi, M. C. (1); Forette, F.
CORPORATE SOURCE: (1) Serv. Pharmacie, Hopital Broca, 54-56 rue Pascal, 75013 Paris France
SOURCE: Journal de Pharmacologie Clinique, [illegible], No. 3, pp. 169-187. ISSN: 0291-1981.
DOCUMENT TYPE: Article
LANGUAGE: French
SUMMARY LANGUAGE: French; English
AB Alzheimer's disease, degenerative disease leading to dementia, associated with anatomo-pathologic and neurochemical modifications which induce a deterioration of the cholinergic system. The main clinical signs are: cognitive distress, intellectual **confusion** and performance difficulties. Psychometric tests as MMSE (mini mental state examination) and Adas-Cog (cognitive function of Alzheimer's disease assessment scale) can evaluate the cognitive functions. Tacrine (Cognex), the first inhibitor of acetylcholinesterase. The treatments were: 40 mg daily of tacrine for 6 weeks, 80 mg/d next 6 weeks, 120 mg/d for 2 months and finally 160 mg/d. The aim of our work was to analyse the